ATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
23058 PC 1		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK00/00205	19/04/2000	23/04/1999

International Patent Classification (IPC) or national classification and IPC

C12N15/24

Applicant

M&E BIOTECH A/S et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22/08/2000	24.08.2001
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Grosskopf, R Telephone No. +49 89 2399 8714

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK00/00205

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)):*

Description, pages:

1-97 as originally filed

Claims, No.:

1-68 as received on 27/04/2001 with letter of 27/04/2001

Drawings, sheets:

1/7-7/7 as originally filed

Sequence listing part of the description, pages:

1-51, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☒ contained in the international application in written form.
   - ☒ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK00/00205

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-32,53-56, 60-68.

because:

   ☒ the said international application, or the said claims Nos. 1-32,53-56, 60-68 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☒ the claims, or said claims Nos. 33-52, 57,58,65-68 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;

citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-32, 53-56,59-64
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-32, 53-56,59-64
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	59
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Ad item III, V and VIII:

The present application is based on the concept to introduce into an animal a modified IL5 molecule said molecule being modified in a manner which induces the production of antibodies against the (mature) IL5 in said animal thereby achieving a down-regulation of IL5 activity.
This concept is not disclosed in the prior art.

According to the Applicant the concept alone constitutes the invention whereas, as should be demonstrated by the additionally submitted literature, the means for carrying out said invention may be obtained by routine or standard procedures

Nevertheless, as far as all claims are concerned the (or an) essential feature is of course the modified IL5 which must not only be capable of inducing the production of antibodies but additionally in order to solve the underlying technical problem **should down-regulate the interleukin 5 (IL5) activity.**

With respect to the (independent) product claims this essential feature does not even form part of the claim.
The same applies for the composition claims which, moreover, do not comprise the "limiting" technical features of the product claim.
Thus, these claims (and consequently all other product claims) lack the essential feature and, in view of Applicant's submissions are not even longer characterised by the desired result to be achieved.
Thus, in the context of the alleged invention the relevance of these claims is unclear (this applies for Claims 33 and 34 but also for Claims 35 to 52 and 57 to 59 which relate thereto).

In addition, even the new features introduced into the product claim still render the determination of the scope of the claims difficult or impossible (which IL5 should be used as a reference to produce a "derivative" and which animal should be used? Which of the several "proposals" mentioned in the claims should a skilled person follow in order to prepare an "analogue"?).

Thus, an examination of accordingly characterised products is still impossible,

especially when considered in the light of the following observations which are also of relevance for the method claims.

Thus, even if it is accepted that the alleged invention is based on an "idea", it has to be notified that the claims are drafted much too broad.
Thus, with respect to all possible analogues which are proposed in the dependent method claims, a skilled person has no guidance which of said possibilities he or she should preferably follow. The analogues which actually have been prepared do not reflect in any reasonable manner the scope of the claims.
Moreover, when taking into account of the contents of the description, it is clear that even within the small number of IL5 analogues which have been prepared those which are in the position to induce antibodies do not necessarily down-regulate IL5 activity (see page 94), i.e. they are not suitable for the desired purpose.
In fact from the myriad of possible "potential" analogues the desired purpose seems to have been demonstrated only by one specific analogue.
Also the additionally submitted documents are not necessarily suitable to overcome these objections.
In fact, if it is or were that simple to produce analogues which induce autoimmunisation why then in the application can only be found one mutant which allegedly is capable of down-regulating IL5 activity?
This Authority is further not in the position to ignore several statements in the application itself which seem to support the view that the breadth of the claims is unjustified when considering the limited number of successful experiments.

In this context we only would like to refer to some passages e.g. page 91 ("this result is not a firm confirmation that the antisera cross-reacts..." let alone down-regulate IL5!) or page 92 lines 13 to 17 and especially page 94 lines 13 to 15.

All of these (and not only these) passages seem to confirm that the alleged "conceptual" invention is not sufficiently supported by convincing experimental evidence and, consequently, the scope of the claims (especially but not exclusively the product claims) is much too broad.

For the assessment of the present claims 1-32, 53-56 an 60-68 on the question

whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

PLOUGMANN, VINGTOFT & PARTNERS A/S
Sankt Annæ Plads 11
Post Office Box 3007
DK-1021 Copenhagen K
DANEMARK

Date of mailing (day/month/year)
~~29 January 2002 (29.01.02)~~

Applicant's or agent's file reference
23058 PC 1

IMPORTANT NOTIFICATION

International application No.
PCT/DK00/00205

International filing date (day/month/year)
19 April 2000 (19.04.00)

1. The following indications appeared on record concerning:
☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address
PLOUGMANN, VINGTOFT & PARTNERS A/S
Sankt Annæ Plads 11
P.O. Box 3007
DK-1021 Copenhagen K
Denmark

State of Nationality:
State of Residence:
Telephone No.: +45 33 63 93 00
Facsimile No.: +45 33 63 96 00
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:
☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
PLOUGMANN & VINGTOFT A/S
Sankt Annæ Plads 11
P.O. Box 3007
DK-1021 Copenhagen K
Denmark

State of Nationality:
State of Residence:
Telephone No.: +45 33 63 93 00
Facsimile No.: +45 33 63 96 00
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:
☒ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Jaime LEITAO

Telephone No.: (41-22) 338.83.38

PAT T COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

To:

PLOUGMANN, VINGTOFT & PARTNERS A/S
Sankt Annæ Plads 11
Post Office Box 3007
DK-1021 Copenhagen K
DANEMARK

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year)
09 October 2001 (09.10.01)

Applicant's or agent's file reference
23058 PC 1

IMPORTANT NOTIFICATION

International application No.
PCT/DK00/00205

International filing date (day/month/year)
19 April 2000 (19.04.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
M & E BIOTECH A/S
Kogle Allé 6
DK-2970 Hørsholm
Denmark

State of Nationality: DK
State of Residence: DK
Telephone No.: +45 45162525
Facsimile No.: +45 45162500
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
PHARMEXA A/S
Kogle Allé 6
DK-2970 Hørsholm
Denmark

State of Nationality: DK
State of Residence: DK
Telephone No.: +45 45162525
Facsimile No.: +45 45162500
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Céline Faust

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) ~~29 January 2001 (29.01.01)~~	
International application No. PCT/DE00/01416	**Applicant's or agent's file reference** PCT/Brand
International filing date (day/month/year) 02 May 2000 (02.05.00)	**Priority date** (day/month/year) 30 April 1999 (30.04.99)
Applicant BRAND, Karsten et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

29 November 2000 (29.11.00)

[ ] in a notice effecting later election filed with the International Bureau on:

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JUL 31 2003
TECH CENTER 1600/2900

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

R. Forax

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing:	
02 November 2000 (02.11.00)	
International application No.: PCT/DK00/00205	Applicant's or agent's file reference: 23058 PC 1
International filing date: 19 April 2000 (19.04.00)	Priority date: 23 April 1999 (23.04.99)
Applicant: KLYSNER, Steen	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

22 August 2000 (22.08.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer:
J. Zahra
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
23058 PC 1		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/DK 00/ 00205	19/04/2000	23/04/1999
Applicant		
M&E BIOTECH A/S et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 4

[X] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

Inter... nal Application No
PCT/DK 00/00205

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/24 A61K39/00 A61K39/385 A61K39/39 A61K31/70
A61K48/00 C07K14/54 C12N1/21 C12N1/19 C12N5/10
C12N15/70 C12N15/86 G01N33/68 A61P37/00 //A61K39/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EMBASE, WPI Data, PAJ, EPO-Internal, STRAND

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 45448 A (BRESAGEN LTD.) 4 December 1997 (1997-12-04) cited in the application page 15, line 5 -page 16, line 2 claims --- -/--	1-7, 9-12,14, 15,17, 18, 21-25, 32-37, 61,62, 65-68

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 June 2000	29/06/2000

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
Nooij, F

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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CM	Cameroon			PL	Poland		
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CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 05849 A (MOURITSEN & ELSNER A/S) 2 March 1995 (1995-03-02) the whole document	1-7, 9-12,14, 15,17, 18, 21-25, 32-37, 61,62, 65-68
A	WO 98 17799 A (THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA ET AL.) 30 April 1998 (1998-04-30) claims	27-31, 38-59
A	WO 97 00321 A (COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION) 3 January 1997 (1997-01-03) examples claims	1-68
A	WO 98 47923 A (TANOX BIOSYSTEMS INC.) 29 October 1998 (1998-10-29) examples claims	1-68
A	WO 95 31480 A (S.P.I. SYNTHETIC PEPTIDES INC.) 23 November 1995 (1995-11-23) claims	1-68
A	WO 95 26365 A (UNITED BIOMEDICAL INC.) 5 October 1995 (1995-10-05) examples claims	1-53
A	K. TAKATSU: "Interleukin 5 and B cell differentiation." CYTOKINE AND GROWTH FACTOR REVIEWS, vol. 9, no. 1, March 1998 (1998-03), pages 25-35, XP002119733 the whole document	1-68
A	J. WELTMAN ET AL.: "Interleukin-5: a proeosinophil cytokine mediator of inflammation in asthma and a target for antisense therapy." ALLERGY AND ASTHMA PROCEEDINGS, vol. 19, no. 5, September 1998 (1998-09), pages 257-261, XP002119734 Province, RI, USA abstract	1-68

-/--

International Application No
PCT/DK 00/00205

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	D. BROIDE ET AL.: "Intradermal gene vaccination down-regulates both arms of the allergic response." JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, vol. 99, no. 1 part 2, January 1997 (1997-01), page S129 XP002119735 St. Louis, MO, USA abstract 523 ------	27-31, 38-59

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9745448 A	04-12-1997	AU 2758497 A	05-01-1998
		EP 0904293 A	31-03-1999
WO 9505849 A	02-03-1995	AT 162723 T	15-02-1998
		AU 707083 B	01-07-1999
		AU 7009198 A	30-07-1998
		AU 7608094 A	21-03-1995
		CA 2170236 A	02-03-1995
		DE 69408342 D	05-03-1998
		DE 69408342 T	14-05-1998
		DK 752886 T	04-05-1998
		EP 0752886 A	15-01-1997
		ES 2112559 T	01-04-1998
		GR 3026419 T	30-06-1998
		JP 9505031 T	20-05-1997
WO 9817799 A	30-04-1998	AU 5002297 A	15-05-1998
		BR 9712852 A	16-11-1999
		EP 0958364 A	24-11-1999
WO 9700321 A	03-01-1997	AU 5991796 A	15-01-1997
WO 9847923 A	29-10-1998	AU 7132098 A	13-11-1998
WO 9531480 A	23-11-1995	AU 708472 B	05-08-1999
		AU 2441895 A	05-12-1995
		CA 2190494 A	23-11-1995
		EP 0759941 A	05-03-1997
		JP 10504018 T	14-04-1998
		US 5824483 A	20-10-1998
WO 9526365 A	05-10-1995	AU 2195395 A	17-10-1995
		CA 2186595 A	05-10-1995
		CN 1146772 A	02-04-1997
		EP 0811016 A	10-12-1997
		JP 9510975 T	04-11-1997

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

by fax and post

PCT

To:

PLOUGMANN, VINGTOFF & PARTNERS A/S
Sankt Annae Plads 11
P.O. Box 3007
DK-1061 COPENHAGEN K
DANEMARK
FAX NO: 33639600

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year)	24.08.2001

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
23058 PC 1	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/DK00/00205	19/04/2000	23/04/1999

Applicant
M&E BIOTECH A/S et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international applicatio

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of th report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation mus contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
23058 PC 1		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/DK00/00205	19/04/2000	23/04/1999

International Patent Classification (IPC) or national classification and IPC
C12N15/24

Applicant
M&E BIOTECH A/S et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report
   II ☐ Priority
   III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☐ Lack of unity of invention
   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   VI ☐ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22/08/2000	24.08.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Grosskopf, R Telephone No. +49 89 2399 8714

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK00/00200

I. **Basis of the report**

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

~~1-37 as originally filed~~

Claims, No.:

1-68 as received on 27/04/2001 with letter of 27/04/2001

Drawings, sheets:

1/7-7/7 as originally filed

Sequence listing part of the description, pages:

1-51, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK00/002(

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have bee considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to thi report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   - ☐ the entire international application.
   - ☒ claims Nos. 1-32,53-56, 60-68.

because:

- ☒ the said international application, or the said claims Nos. 1-32,53-56, 60-68 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
  see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☒ the claims, or said claims Nos. 33-52, 57,58,65-68 are so inadequately supported by the description that n meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   - ☐ the written form has not been furnished or does not comply with the standard.
   - ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK00/002(

citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-32, 53-56,59-64
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-32, 53-56,59-64
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	59
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether th claims are fully supported by the description, are made:
see separate sheet

Ad item III, V and VIII:

The present application is based on the concept to introduce into an animal a modified IL5 molecule said molecule being modified in a manner which induces the production of antibodies against the (mature) IL5 in said animal thereby achieving a down-regulation of IL5 activity.
This concept is not disclosed in the prior art.

According to the Applicant the concept alone constitutes the invention whereas, as should be demonstrated by the additionally submitted literature, the means for carrying out said invention may be obtained by routine or standard procedures

Nevertheless, as far as all claims are concerned the (or an) essential feature is of course the modified IL5 which must not only be capable of inducing the production of antibodies but additionally in order to solve the underlying technical problem **should down-regulate the interleukin 5 (IL5) activity.**

With respect to the (independent) product claims this essential feature does not even form part of the claim.
The same applies for the composition claims which, moreover, do not comprise the "limiting" technical features of the product claim.
Thus, these claims (and consequently all other product claims) lack the essential feature and, in view of Applicant's submissions are not even longer characterised by the desired result to be achieved.
Thus, in the context of the alleged invention the relevance of these claims is unclear (this applies for Claims 33 and 34 but also for Claims 35 to 52 and 57 to 59 which relate thereto).

In addition, even the new features introduced into the product claim still render the determination of the scope of the claims difficult or impossible (which IL5 should be used as a reference to produce a "derivative" and which animal should be used? Which of th several "proposals" mentioned in the claims should a skilled person follow in order to prepare an "analogue"?).

Thus, an examination f accordingly characterised products is still impossibl ,

especially when considered in the light of the following observations which are also of relevance for the method claims.

Thus, even if it is accepted that the alleged invention is based on an "idea", it has to be notified that the claims are drafted much too broad.
Thus, with respect to all possible analogues which are proposed in the dependent method claims, a skilled person has no guidance which of said possibilities he or she should preferably follow. The analogues which actually have been prepared do not reflect in any reasonable manner the scope of the claims.
Moreover, when taking into account of the contents of the description, it is clear that even within the small number of IL5 analogues which have been prepared those which are in the position to induce antibodies do not necessarily down-regulate IL5 activity (see page 94), i.e. they are not suitable for the desired purpose.
In fact from the myriad of possible "potential" analogues the desired purpose seems to have been demonstrated only by one specific analogue.
Also the additionally submitted documents are not necessarily suitable to overcome these objections.
In fact, if it is or were that simple to produce analogues which induce autoimmunisation why then in the application can only be found one mutant which allegedly is capable of down-regulating IL5 activity?
This Authority is further not in the position to ignore several statements in the application itself which seem to support the view that the breadth of the claims is unjustified when considering the limited number of successful experiments.

In this context we only would like to refer to some passages e.g. page 91 ("this result is not a firm confirmation that the antisera cross-reacts..." let alone down-regulate IL5!) or page 92 lines 13 to 17 and especially page 94 lines 13 to 15.

All of these (and not only these) passages seem to confirm that the alleged "conceptual" invention is not sufficiently supported by convincing experimental evidence and, consequently, the scope of th claims (especially but not exclusively the product claims) is much too broad.

For the assessment of the present claims 1-32, 53-56 an 60-68 on the question

whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicabl the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

09/980916
JC13 Rec'd PCT/PTO 23 OCT 2001

Amended claims

1. A method for *in vivo* down-regulation of interleukin 5 (IL5) activity in an animal, including a human being, the method comprising effecting presentation to the animal's immune system of an immunogenically effective amount of

- at least one IL5 polypeptide autologous in the animal or a subsequence thereof which has been formulated so that immunization of the animal with the autologous IL5 polypeptide or subsequence thereof induces production by the animal of antibodies against the IL5 polypeptide, and/or
- at least one IL5 analogue wherein is introduced at least one modification in the amino acid sequence of the animal's autologous IL5 polypeptide which has as a result that immunization of the animal with the analogue induces production of antibodies in the animal against the animal's autologous IL5 polypeptide.

2. The method according to claim 1, wherein is presented an IL5 analogue with at least one modification of the IL5 amino acid sequence.

3. The method according to claim 2, wherein the modification has as a result that a substantial fraction of IL5 B-cell epitopes are preserved and that

- at least one foreign T helper lymphocyte epitope (T_H epitope) is introduced, and/or
- at least one first moiety is introduced which effects targeting of the modified molecule to an antigen presenting cell (APC) or a B-lymphocyte, and/or
- at least one second moiety is introduced which stimulates the immune system, and/or
- at least one third moiety is introduced which optimizes presentation of the modified IL5 polypeptide to the immune system.

4. The method according to claim 3, wherein the modification includes introduction as side groups, by covalent or non-covalent binding to suitable chemical groups in IL5 or a subsequence thereof, of the foreign T_H epitope and/or of the first and/or of the second and/or of the third moiety.

5. The method according to claim 3 or 4, wherein the modification includes amino acid substitution and/or deletion and/or insertion and/or addition.

6. The method according to claim 5, wherein the modification results in th provision of a fusion polypeptide.

7. The method according to claim 5 or 6, wherein introduction of the amino acid substitution and/or deletion and/or insertion and/or addition results in a substantial preservation of the overall tertiary structure of IL5.

8. The method according to any one of claims 2-7, wherein the modification includes duplication of at least one IL5 B-cell epitope and/or introduction of a hapten.

9. The method according to any one of claims 3-8, wherein the foreign T-cell epitope is immunodominant in the animal.

10. The method according to any one of claims 3-9, wherein the foreign T-cell epitope is promiscuous.

11. The method according to claim 10, wherein the at least one foreign T-cell epitope is selected from a natural promiscuous T-cell epitope and an artificial MHC-II binding peptide sequence.

12. The method according to claim 11, wherein the natural T-cell epitope is selected from a Tetanus toxoid epitope such as P2 or P30, a diphtheria toxoid epitope, an influenza virus hemagluttinin epitope, and a *P. falciparum* CS epitope.

13. The method according to any one of claims 3-12, wherein the first moiety is a substantially specific binding partner for a B-lymphocyte specific surface antigen or for an APC specific surface antigen, such as a hapten or a carbohydrate for which there is a receptor on the B-lymphocyte or the APC.

14. The method according to any one of claims 3-13, wherein the second moiety is selected from a cytokine, a hormone, and a heat-shock protein.

15. The method according to claim 6, wherein the cytokine is selected from, or is an effective part of, interferon γ (IFN-γ), Flt3L, interleukin 1 (IL-1), interleukin 2 (IL-2), interleukin 4 (IL-4), interleukin 6 (IL-6), interleukin 12 (IL-12), interleukin 13 (IL-13), interleukin 15 (IL-15), and granulocyte-macrophage colony stimulating factor (GM-CSF), and the heat-shock protein is selected from, or is an effective part of any of, HSP70, HSP90, HSC70, GRP94, and calreticulin (CRT).

16. The method according to any one of claims 3-15, wherein the third moiety is of lipid nature, such as a palmitoyl group, a myristyl group, a farnesyl group, a geranyl-geranyl group, a GPI-anchor, and an N-acyl diglyceride group.

17. The method according to any one of the preceding claims, wherein the IL5 polypeptide has been modified in at least one of loops 1-3 or in the amino acid residues C-terminal to helix D, said loops and said helix D corresponding to those shown in Fig. 3 for human and murine IL5.

18. The method according to claim 17, wherein the IL5 polypeptide is a human IL5 polypeptide.

19. The method according to claim 18, wherein the human IL5 polypeptide has been modified by substituting at least one amino acid sequence in SEQ ID NO: 1 with at least one amino acid sequence of equal or different length thereby giving rise to a foreign T_H epitope, wherein substituted amino acid residues are selected from the group consisting of residues 87-90, residues 88-91, residues 32-43, residues 33-43, residues 59-64, residues 86-91, and residues 110-113.

20. The method according to any one of the preceding claims, wherein presentation to the immune system is effected by having at least two copies of the IL5 polypeptide, the subsequence thereof or the modified IL5 polypeptide covalently of non-covalently linked to a carrier molecule capable of effecting presentation of multiple copies of antigenic determinants.

21. The method according to any the preceding claims, wherein the IL5 polypeptide, the subsequence thereof, or the modified IL5 polypeptide has been formulated with an adjuvant which facilitates breaking of autotolerance to autoantigens.

22. The method according to claim 21, wherein the adjuvant is selected from the group consisting of an immune targeting adjuvant; an immune modulating adjuvant such as a toxin, a cytokine and a mycobacterial derivative; an oil formulation; a polymer; a micelle forming adjuvant; a saponin; an immunostimulating complex matrix (an ISCOM matrix); a particle; DDA; aluminium adjuvants; DNA adjuvants; γ-inulin; and an encapsulating adjuvant.

23. The method according to any one of the preceding claims, wherein an effective amount of the IL5 polypeptide or the IL5 analogue is administered to the animal via a route selected from the parenteral route such as the intradermal, the subdermal, the intracutaneous, the subcutaneous, and the intramuscular routes; the peritoneal route; the oral route; the buccal route; the sublingual route; the epidural route; the spinal route; the anal route; and the intracranial route.

24. The method according to claim 23, wherein the effective amount is between 0.5 µg and 2,000 µg of the IL5 polypeptide, the subsequence thereof or the analogue thereof.

25. The method according to claim 23 or 24, which includes at least one administration of the IL5 polypeptide or analogue per year, such as at least 2, at least 3, at least 4, at least 8, and at least 12 administrations per year.

26. The method according to any one of claims 23-25, wherein the IL5 polypeptide or analogue is contained in a virtual lymph node (VLN) device.

27. The method according to any one of claims 1-20, wherein presentation of modified IL5 to the immune system is effected by introducing nucleic acid(s) encoding the modified IL5 into the animal's cells and thereby obtaining *in vivo* expression by the cells of the nucleic acid(s) introduced.

28. The method according to claim 27, wherein the nucleic acid(s) introduced is/are selected from naked DNA, DNA formulated with charged or uncharged lipids, DNA formulated in liposomes, DNA included in a viral vector, DNA formulated with a transfection-facilitating protein or polypeptide, DNA formulated with a targeting protein or polypeptide, DNA formulated with Calcium precipitating agents, DNA coupled to an inert carrier molecule, DNA encapsulated in chitin or chitosan, and DNA formulated with an adjuvant such as the adjuvants defined in claim 22.

29. The method according to claim 27 or 28, wherein the nucleic acids are administered intraarterially, intravenously, or by the routes defined in claim 23.

30. The method according to claim 28 or 29, wherein the nucleic acid(s) is/are contained in a VLN device.

31. The method according to any one of claims 28-30, which includes at least one administration of the nucleic acids per year, such as at least 2, at least 3, at least 4, at least 6, and at least 12 administrations per year

32. A method for treating and/or preventing and/or ameliorating asthma or other chronic allergic conditions characterized by eosinophilia, the method comprising down-regulating IL5 activity according to the method of any one of claims 1-31 to such an extent that the number of eosinophil cells, either systemically or locally at the disease focus, is significantly reduced, such as a reduction of at least 20%.

33. An IL5 analogue which is derived from an animal IL5 polypeptide wherein is introduced a modification which has as a result that immunization of the animal with the analogue induces production of antibodies against the IL5 polypeptide, and wherein the modification involves amino acid substitution and/or insertion and/or deletion to any one of loops 1-3 or C-terminally to helix D in IL5.

34. An IL5 analogue according to claim 33, wherein the modification is as defined in any one of claims 2-20.

35. An immunogenic composition comprising an immunogenically effective amount of an IL5 polypeptide autologous in an animal, said IL5 polypeptide being formulated together with an immunologically acceptable adjuvant so as to break the animal's autotolerance towards the IL5 polypeptide, the composition further comprising a pharmaceutically and immunologically acceptable carrier and/or vehicle.

36. An immunogenic composition comprising an immunogenically effective amount of an IL5 analogue according to claim 33 or 34, the composition further comprising a pharmaceutically and immunologically acceptable carrier and/or vehicle and optionally an adjuvant.

37. An immunogenic composition according to Claim 35 or 36, wherein the adjuvant is selected from the group consisting of the adjuvants of claim 22.

38. A nucleic acid fragment which encodes an IL5 analogue according to claim 33 or 34.

39. A vector carrying th nucleic acid fragment according to claim 38.

40. The vector according to claim 39 which is capable of autonomous replication.

41. The vector according to claim 39 or 40 which is selected from the group consisting of a plasmid, a phage, a cosmid, a mini-chromosome, and a virus.

42. The vector according to any one of claims 39-41, comprising, in the 5'→3' direction and in operable linkage, a promoter for driving expression of the nucleic acid fragment according to claim 38, optionally a nucleic acid sequence encoding a leader peptide enabling secretion of or integration into the membrane of the polypeptide fragment, the nucleic acid fragment according to claim 38, and optionally a terminator.

43. The vector according to any one of claims 39-42 which, when introduced into a host cell, is integrated in the host cell genome.

44. The vector according to any one of claims 39-42 which, when introduced into a host cell, is not capable of being integrated in the host cell genome.

45. The vector according to any one of claims 39-44, wherein the promoter drives expression in a eukaryotic cell and/or in a prokaryotic cell.

46. A transformed cell carrying the vector of any one of claims 39-45.

47. The transformed cell according to claim 46 which is capable of replicating the nucleic acid fragment according to claim 38.

48. The transformed cell according to claim 47, which is a microorganism selected from a bacterium, a yeast, a protozoan, or a cell derived from a multicellular organism selected from a fungus, an insect cell such as an S_2 or an SF cell, a plant cell, and a mammalian cell.

49. The transformed cell according to claim 48 which is a bacterium of the genus *Escherichia*, *Bacillus*, *Salmonella*, or *Mycobacterium*.

50. The transformed cell according to claim 52, which is selected from the group consisting of an *E. coli* cell, and a non-pathogenic *Mycobacterium* cell such as *M. bovis* BCG.

51. The transformed cell according to any one of claims 46-50, which expresses the nucleic acid fragment according to claim 38.

52. The transformed cell according to claim 55, which secretes or carries on its surface, the IL5 analogue according to claim 33 or 34.

53. The method according to any one of claims 1-20, wherein presentation to the immune system is effected by administering a non-pathogenic microorganism or virus which is carrying a nucleic acid fragment which encodes and expresses the IL5 polypeptide or analogue.

54. The method according to claim 53, wherein the virus is a non-virulent pox virus such as a vaccinia virus.

55. The method according to claim 54, wherein the microorganism is a bacterium, such as a bacterium defined in claim 49 or 50.

56. The method according to any one of claims 53-55, wherein the non-pathogenic microorganism or virus is administered one single time to the animal.

57. A composition for inducing production of antibodies against IL5, the composition comprising

- a nucleic acid fragment according to claim 38 or a vector according to any one of claims 39-45, and
- a pharmaceutically and immunologically acceptable carrier and/or vehicle and/or adjuvant.

58. The composition according to claim 57, wherein the nucleic acid fragment is formulated according to claim 28 or 30.

59. A stable cell line which carries the vector according to any one of claims 39-45 and which expresses the nucleic acid fragment according to claim 38, and which optionally secretes or carries the IL5 analogue according to claim 33 or 34 on its surface.

60. A method for the preparation of the cell according to any on of claims 46-52, the method comprising transforming a host cell with the nucleic acid fragment according to claim 38 or with the vector according to any one of claims 39-45.

61. A method for the identification of a modified IL5 polypeptide which is capable of inducing antibodies against unmodified IL5 in an animal species where the unmodified IL5 polypeptide is a self-protein, the method comprising

- preparing, by means of peptide synthesis or genetic engineering techniques, a set of mutually distinct modified IL5 polypeptides wherein amino acids have been added to, inserted in, deleted from, or substituted into the amino acid sequence of an IL5 polypeptide of the animal species thereby giving rise to amino acid sequences in the set which comprise T-cell epitopes which are foreign to the animal species, or preparing a set of nucleic acid fragments encoding the set of mutually distinct modified IL5 polypeptides,
- testing members of the set for their ability to induce production of antibodies by the animal species against the unmodified IL5, and
- identifying and optionally isolating the member(s) of the set which significantly induces antibody production against unmodified IL5 in the animal species, or identifying and optionally isolating the polypeptide expression products encoded by embers of the set of nucleic acid fragments which significantly induces antibody production against unmodified IL5 in the animal species.

62. A method for the preparation of an immunogenic composition comprising at least one modified IL5 polypeptide which is capable of inducing antibodies against unmodified IL5 in an animal species where the unmodified IL5 polypeptide is a self-protein, the method comprising

- preparing, by means of peptide synthesis or genetic engineering techniques, a set of mutually distinct modified IL5 polypeptides wherein amino acids have been added to, inserted in, deleted from, or substituted into the amino acid sequence of an IL5 polypeptide of the animal species thereby giving rise to amino acid sequences in the set comprising T-cell epitopes which are foreign to the animal,
- testing members of the set for their ability to induce production of antibodies by the animal species against the unmodified IL5, and
- admixing the member(s) of the set which significantly induces production of antibodies in the animal species which are reactive with IL5 with a pharmaceutically and immunologically acceptable carrier and/or vehicle, optionally in combination with at least one pharmaceutically and immunologically acceptable adjuvant.

63. The method according to claim 61 or 62, wherein preparation of the members of the set comprises preparation of mutually distinct nucleic acid sequences, each sequence being a nucleic acid sequence according to claim 38, insertion of the nucleic acid sequences into appropriate expression vectors, transformation of suitable host cells with the vectors, and expression of the nucleic acid sequences, optionally followed by isolation of the expression products.

64. The method according to claim 63, wherein the preparation of the nucleic acid sequences and/or the vectors is achieved by the aid of a molecular amplification technique such as PCR, or by the aid of nucleic acid synthesis.

65. Use of IL5 or a subsequence thereof for the preparation of an immunogenic composition comprising an adjuvant for down-regulating IL5 activity in an animal.

66. Use of IL5 or a subsequence thereof for the preparation of an immunogenic composition comprising an adjuvant for the treatment, prophylaxis or amelioration of asthma or other chronic allergic conditions.

67. Use of an IL5 analogue for the preparation of an immunogenic composition optionally comprising an adjuvant for down-regulating IL5 activity in an animal.

68. Use of an IL5 analogue for the preparation of an immunogenic composition optionally comprising an adjuvant for the treatment, prophylaxis or amelioration of asthma or other chronic allergic conditions.

CLAIMS

1. A method for *in vivo* down-regulation of interleukin 5 (IL5) activity in an animal, including a human being, the method comprising effecting presentation to the animal's immune system of an immunogenically effective amount of

- at least one IL5 polypeptide or subsequence thereof which has been formulated so that immunization of the animal with the IL5 polypeptide or subsequence thereof induces production of antibodies against the IL5 polypeptide, and/or
- at least one IL5 analogue wherein is introduced at least one modification in the IL5 amino acid sequence which has as a result that immunization of the animal with the analogue induces production of antibodies against the IL5 polypeptide.

2. The method according to claim 1, wherein is presented an IL5 analogue with at least one modification of the IL5 amino acid sequence.

3. The method according to claim 2, wherein the modification has as a result that a substantial fraction of IL5 B-cell epitopes are preserved and that

- at least one foreign T helper lymphocyte epitope (T_H epitope) is introduced, and/or
- at least one first moiety is introduced which effects targeting of the modified molecule to an antigen presenting cell (APC) or a B-lymphocyte, and/or
- at least one second moiety is introduced which stimulates the immune system, and/or
- at least one third moiety is introduced which optimizes presentation of the modified IL5 polypeptide to the immune system.

4. The method according to claim 3, wherein the modification includes introduction as side groups, by covalent or non-covalent binding to suitable chemical groups in IL5 or a subse-

quence thereof, of the foreign T_H epitope and/or of the first and/or of the second and/or of the third moiety.

5. The method according to claim 3 or 4, wherein the modification includes amino acid substitution and/or deletion and/or insertion and/or addition.

6. The method according to claim 5, wherein the modification results in the provision of a fusion polypeptide.

7. The method according to claim 5 or 6, wherein introduction of the amino acid substitution and/or deletion and/or insertion and/or addition results in a substantial preservation of the overall tertiary structure of IL5.

8. The method according to any one of claims 2-7, wherein the modification includes duplication of at least one IL5 B-cell epitope and/or introduction of a hapten.

9. The method according to any one of claims 3-8, wherein the foreign T-cell epitope is immunodominant in the animal.

10. The method according to any one of claims 3-9, wherein the foreign T-cell epitope is promiscuous.

11. The method according to claim 10, wherein the at least one foreign T-cell epitope is selected from a natural promiscuous T-cell epitope and an artificial MHC-II binding peptide sequence.

12. The method according to claim 11, wherein the natural T-cell epitope is selected from a Tetanus toxoid epitope such as P2 or P30, a diphtheria toxoid epitope, an influenza virus hemagluttinin epitope, and a *P. falciparum* CS epitope.

13. The method according to any one of claims 3-12, wherein the first moiety is a substantially specific binding partner for a B-lymphocyte specific surface antigen or for an APC spe-

cific surface antigen, such as a hapten or a carbohydrate for which there is a receptor on the B-lymphocyte or the APC.

14. The method according to any one of claims 3-13, wherein the second moiety is selected from a cytokine, a hormone, and a heat-shock protein.

15. The method according to claim 6, wherein the cytokine is selected from, or is an effective part of, interferon γ (IFN-γ), Flt3L, interleukin 1 (IL-1), interleukin 2 (IL-2), interleukin 4 (IL-4), interleukin 6 (IL-6), interleukin 12 (IL-12), interleukin 13 (IL-13), interleukin 15 (IL-15), and granulocyte-macrophage colony stimulating factor (GM-CSF), and the heat-shock protein is selected from, or is an effective part of any of, HSP70, HSP90, HSC70, GRP94, and calreticulin (CRT).

16. The method according to any one of claims 3-15, wherein the third moiety is of lipid nature, such as a palmitoyl group, a myristyl group, a farnesyl group, a geranyl-geranyl group, a GPI-anchor, and an N-acyl diglyceride group.

17. The method according to any one of the preceding claims, wherein the IL5 polypeptide has been modified in at least one of loops 1-3 or in the amino acid residues C-terminal to helix D, said loops and said helix D corresponding to those shown in Fig. 3 for human and murine IL5.

18. The method according to claim 17, wherein the IL5 polypeptide is a human IL5 polypeptide.

19. The method according to claim 18, wherein the human IL5 polypeptide has been modified by substituting at least one amino acid sequence in SEQ ID NO: 1 with at least one amino acid sequence of equal or different length thereby giving rise to a foreign T_H epitope, wherein substituted amino acid residues are selected from the group consisting of residues 87-90, residues 88-91, residues 32-43, residues 33-43, residues 59-64, residues 86-91, and residues 110-113.

20. The method according to any one of the preceding claims, wherein presentation to the immune system is effected by having at least two copies of the IL5 polypeptide, the subsequence thereof or the modified IL5 polypeptide covalently of non-covalently linked to a carrier molecule capable of effecting presentation of multiple copies of antigenic determinants.

21. The method according to any the preceding claims, wherein the IL5 polypeptide, the subsequence thereof, or the modified IL5 polypeptide has been formulated with an adjuvant which facilitates breaking of autotolerance to autoantigens.

22. The method according to claim 21, wherein the adjuvant is selected from the group consisting of an immune targeting adjuvant; an immune modulating adjuvant such as a toxin, a cytokine and a mycobacterial derivative; an oil formulation; a polymer; a micelle forming adjuvant; a saponin; an immunostimulating complex matrix (an ISCOM matrix); a particle; DDA; aluminium adjuvants; DNA adjuvants; γ-inulin; and an encapsulating adjuvant.

23. The method according to any one of the preceding claims, wherein an effective amount of the IL5 polypeptide or the IL5 analogue is administered to the animal via a route selected from the parenteral route such as the intradermal, the subdermal, the intracutaneous, the subcutaneous, and the intramuscular routes; the peritoneal route; the oral route; the buccal route; the sublinqual route; the epidural route; the spinal route; the anal route; and the intracranial route.

24. The method according to claim 23, wherein the effective amount is between 0.5 µg and 2,000 µg of the IL5 polypeptide, the subsequence thereof or the analogue thereof.

25. The method according to claim 23 or 24, which includes at least one administration of the IL5 polypeptide or analogue

per year, such as at least 2, at least 3, at least 4, at least 6, and at least 12 administrations per year.

26. The method according to any one of claims 23-25, wherein the IL5 polypeptide or analogue is contained in a virtual lymph node (VLN) device.

27. The method according to any one of claims 1-20, wherein presentation of modified IL5 to the immune system is effected by introducing nucleic acid(s) encoding the modified IL5 into the animal's cells and thereby obtaining *in vivo* expression by the cells of the nucleic acid(s) introduced.

28. The method according to claim 27, wherein the nucleic acid(s) introduced is/are selected from naked DNA, DNA formulated with charged or uncharged lipids, DNA formulated in liposomes, DNA included in a viral vector, DNA formulated with a transfection-facilitating protein or polypeptide, DNA formulated with a targeting protein or polypeptide, DNA formulated with Calcium precipitating agents, DNA coupled to an inert carrier molecule, DNA encapsulated in chitin or chitosan, and DNA formulated with an adjuvant such as the adjuvants defined in claim 22.

29. The method according to claim 27 or 28, wherein the nucleic acids are administered intraarterially, intraveneously, or by the routes defined in claim 23.

30. The method according to claim 28 or 29, wherein the nucleic acid(s) is/are contained in a VLN device.

31. The method according to any one of claims 28-30, which includes at least one administration of the nucleic acids per year, such as at least 2, at least 3, at least 4, at least 6, and at least 12 administrations per year

32. A method for treating and/or preventing and/or ameliorating asthma or other chronic allergic conditions characterized

by eosinophilia, the method comprising down-regulating IL5 activity according to the method of any one of claims 1-31 to such an extent that the number of eosinophil cells, either systemically or locally at the disease focus, is significantly reduced, such as a reduction of at least 20%.

33. An IL5 analogue which is derived from an animal IL5 polypeptide wherein is introduced a modification which has as a result that immunization of the animal with the analogue induces production of antibodies against the IL5 polypeptide.

34. An IL5 analogue according to claim 33, wherein the modification is as defined in any one of claims 1-22.

35. An immunogenic composition comprising an immunogenically effective amount of an IL5 polypeptide autologous in an animal, said IL5 polypeptide being formulated together with an immunologically acceptable adjuvant so as to break the animal's autotolerance towards the IL5 polypeptide, the composition further comprising a pharmaceutically and immunologically acceptable carrier and/or vehicle.

36. An immunogenic composition comprising an immunogenically effective amount of an IL5 analogue according to claim 33 or 34, the composition further comprising a pharmaceutically and immunologically acceptable carrier and/or vehicle and optionally an adjuvant.

37. An immunogenic composition according to Claim 35 or 36, wherein the adjuvant is selected from the group consisting of the adjuvants of claim 22.

38. A nucleic acid fragment which encodes an IL5 analogue according to claim 33 or 34.

39. A vector carrying the nucleic acid fragment according to claim 38.

40. The vector according to claim 39 which is capable of autonomous replication.

41. The vector according to claim 39 or 40 which is selected from the group consisting of a plasmid, a phage, a cosmid, a mini-chromosome, and a virus.

42. The vector according to any one of claims 39-41, comprising, in the 5'→3' direction and in operable linkage, a promoter for driving expression of the nucleic acid fragment according to claim 38, optionally a nucleic acid sequence encoding a leader peptide enabling secretion of or integration into the membrane of the polypeptide fragment, the nucleic acid fragment according to claim 38, and optionally a terminator.

43. The vector according to any one of claims 39-42 which, when introduced into a host cell, is integrated in the host cell genome.

44. The vector according to any one of claims 39-42 which, when introduced into a host cell, is not capable of being integrated in the host cell genome.

45. The vector according to any one of claims 39-44, wherein the promoter drives expression in a eukaryotic cell and/or in a prokaryotic cell.

46. A transformed cell carrying the vector of any one of claims 39-45.

47. The transformed cell according to claim 46 which is capable of replicating the nucleic acid fragment according to claim 38.

48. The transformed cell according to claim 47, which is a microorganism selected from a bacterium, a yeast, a protozoan, or a cell derived from a multicellular organism selected from

a fungus, an insect cell such as an S_2 or an SF cell, a plant cell, and a mammalian cell.

49. The transformed cell according to claim 48 which is a bacterium of the genus *Escherichia*, *Bacillus*, *Salmonella*, or *Mycobacterium*.

50. The transformed cell according to claim 52, which is selected from the group consisting of an *E. coli* cell, and a non-pathogenic *Mycobacterium* cell such as *M. bovis* BCG.

51. The transformed cell according to any one of claims 46-50, which expresses the nucleic acid fragment according to claim 38.

52. The transformed cell according to claim 55, which secretes or carries on its surface, the IL5 analogue according to claim 33 or 34.

53. The method according to any one of claims 1-20, wherein presentation to the immune system is effected by administering a non-pathogenic microorganism or virus which is carrying a nucleic acid fragment which encodes and expresses the IL5 polypeptide or analogue.

54. The method according to claim 53, wherein the virus is a non-virulent pox virus such as a vaccinia virus.

55. The method according to claim 54, wherein the microorganism is a bacterium, such as a bacterium defined in claim 49 or 50.

56. The method according to any one of claims 53-55, wherein the non-pathogenic microorganism or virus is administered one single time to the animal.

57. A composition for inducing production of antibodies against IL5, the composition comprising

- a nucleic acid fragment according to claim 38 or a vector according to any one of claims 39-45, and
- a pharmaceutically and immunologically acceptable carrier and/or vehicle and/or adjuvant.

58. The composition according to claim 57, wherein the nucleic acid fragment is formulated according to claim 28 or 30.

59. A stable cell line which carries the vector according to any one of claims 39-45 and which expresses the nucleic acid fragment according to claim 38, and which optionally secretes or carries the IL5 analogue according to claim 33 or 34 on its surface.

60. A method for the preparation of the cell according to any one of claims 46-52, the method comprising transforming a host cell with the nucleic acid fragment according to claim 38 or with the vector according to any one of claims 39-45.

61. A method for the identification of a modified IL5 polypeptide which is capable of inducing antibodies against unmodified IL5 in an animal species where the unmodified IL5 polypeptide is a self-protein, the method comprising

- preparing, by means of peptide synthesis or genetic engineering techniques, a set of mutually distinct modified IL5 polypeptides wherein amino acids have been added to, inserted in, deleted from, or substituted into the amino acid sequence of an IL5 polypeptide of the animal species thereby giving rise to amino acid sequences in the set which comprise T-cell epitopes which are foreign to the animal species, or preparing a set of nucleic acid fragments encoding the set of mutually distinct modified IL5 polypeptides,
- testing members of the set for their ability to induce production of antibodies by the animal species against the unmodified IL5, and

- identifying and optionally isolating the member(s) of the set which significantly induces antibody production against unmodified IL5 in the animal species, or identifying and optionally isolating the polypeptide expression products encoded by embers of the set of nucleic acid fragments which significantly induces antibody production against unmodified IL5 in the animal species.

62. A method for the preparation of an immunogenic composition comprising at least one modified IL5 polypeptide which is capable of inducing antibodies against unmodified IL5 in an animal species where the unmodified IL5 polypeptide is a self-protein, the method comprising

- preparing, by means of peptide synthesis or genetic engineering techniques, a set of mutually distinct modified IL5 polypeptides wherein amino acids have been added to, inserted in, deleted from, or substituted into the amino acid sequence of an IL5 polypeptide of the animal species thereby giving rise to amino acid sequences in the set comprising T-cell epitopes which are foreign to the animal,
- testing members of the set for their ability to induce production of antibodies by the animal species against the unmodified IL5, and
- admixing the member(s) of the set which significantly induces production of antibodies in the animal species which are reactive with IL5 with a pharmaceutically and immunologically acceptable carrier and/or vehicle, optionally in combination with at least one pharmaceutically and immunologically acceptable adjuvant.

63. The method according to claim 61 or 62, wherein preparation of the members of the set comprises preparation of mutually distinct nucleic acid sequences, each sequence being a nucleic acid sequence according to claim 38, insertion of the nucleic acid sequences into appropriate expression vectors, transformation of suitable host cells with the vectors, and

expression of the nucleic acid sequences, optionally followed by isolation of the expression products.

64. The method according to claim 63, wherein the preparation of the nucleic acid sequences and/or the vectors is achieved by the aid of a molecular amplification technique such as PCR, or by the aid of nucleic acid synthesis.

65. Use of IL5 or a subsequence thereof for the preparation of an immunogenic composition comprising an adjuvant for down-regulating IL5 activity in an animal.

66. Use of IL5 or a subsequence thereof for the preparation of an immunogenic composition comprising an adjuvant for the treatment, prophylaxis or amelioration of asthma or other chronic allergic conditions.

67. Use of an IL5 analogue for the preparation of an immunogenic composition optionally comprising an adjuvant for down-regulating IL5 activity in an animal.

68. Use of an IL5 analogue for the preparation of an immunogenic composition optionally comprising an adjuvant for the treatment, prophylaxis or amelioration of asthma or other chronic allergic conditions.

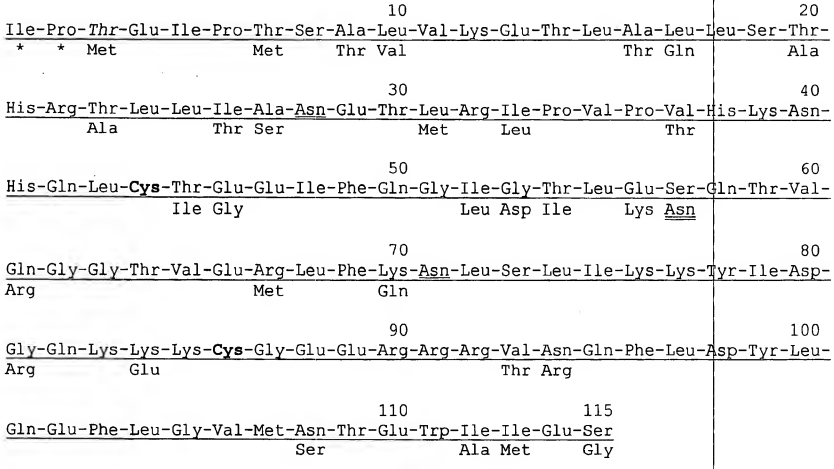
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Fig. 1

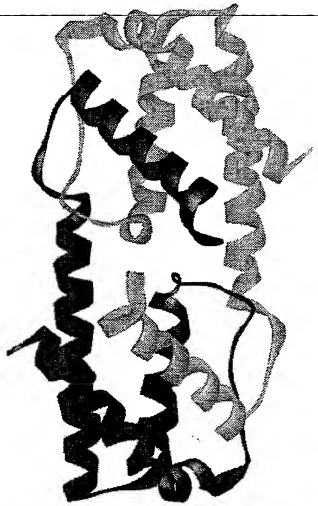


Fig. 2A

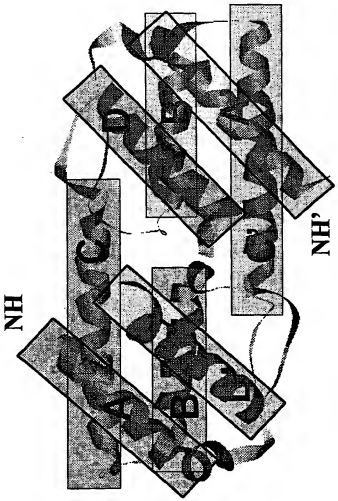


Fig. 2B

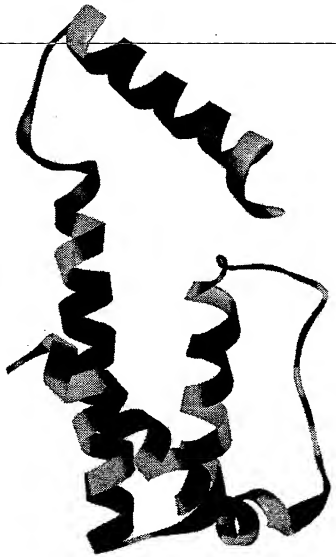
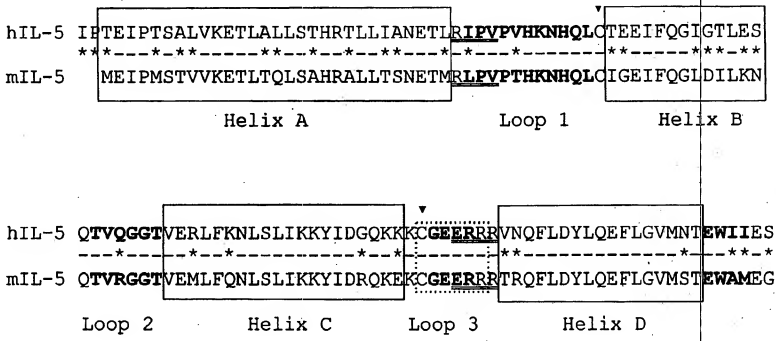


Fig. 2C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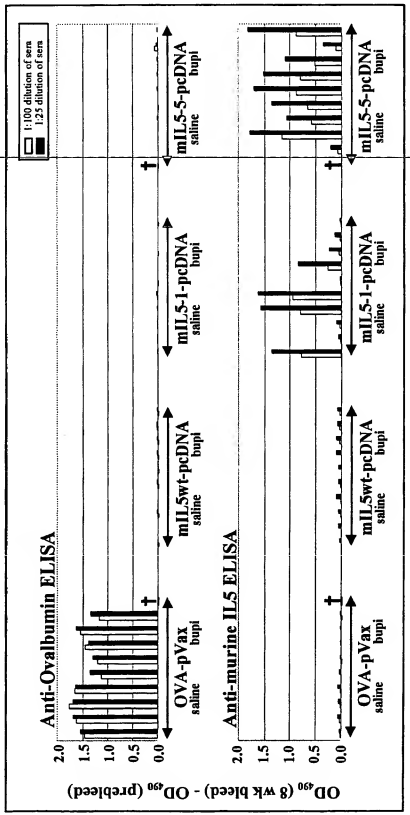
mIL-5 MEIPMSTVVKETLTQLSAHRALLTSNETMRLPVPTHKNHQLCIGEIFQGLDILKN 55
Helix A
Loop 1
Helix B
hIL-5 QTVQGGTVERLFKNLSLIKKYIDGQKKKCGEERRRVNQFLDYLQEFLGVMNTEWIIES 115
mIL-5 QTVRGGTVEMLFQNLSLIKKYIDRQKEKCGEERRRTRQFLDYLQEFLGVMSTEWAMEG 113
Loop 2
Helix C
Loop 3
Helix D

Fig. 3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Anti-murine IL5 ELISA
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1:25 dilution of sera
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2.0
1.5
1.0
0.5
0.0
OVA-pVax
saline
bupi
mIL5wt-pcDNA
mIL5-1-pcDNA
mIL5-5-pcDNA

Fig. 4

Helix
Loop
Cysteine
P2
P30
mIL5wt
mIL5-1
mIL5-5
mIL5-7
mIL5-2
mIL5-4
mIL5-6
mIL5-12
mIL5-13
A
B
C
D
1
2
3

Fig. 5